

# SILVER SALVARSAN

BY

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*(From the Transactions of the Chemical Society, 1923, Vol. 123)*



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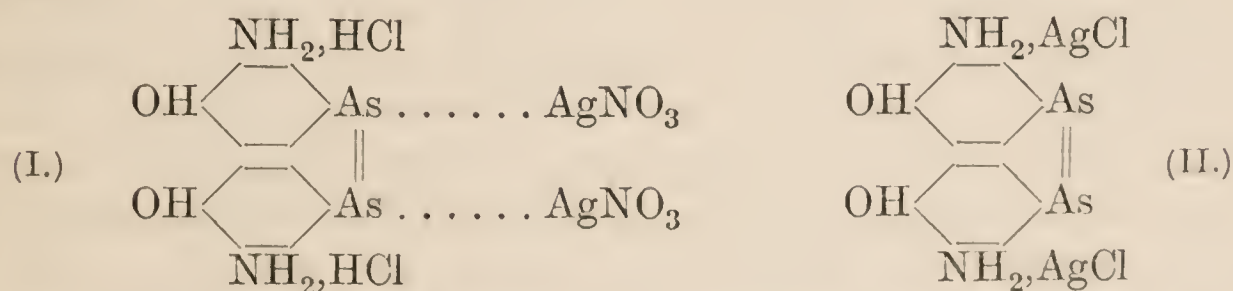


## LXXVI.—*Silver Salvarsan.*

By WILLIAM HERBERT GRAY.

IN 1913, Ehrlich directed attention to the fact that salvarsan (diaminodihydroxyarsenobenzene dihydrochloride) had the remarkable property of forming stable complexes with salts of the heavy metals. In these, the ionic reactions of the metal had disappeared; for instance, they could be made alkaline, and thus suitable for intravenous injection, without losing their solubility. Sodium silver salvarsan (Brit. Pat. 1247/1914) has come into prominence for the treatment of the highly resistant late stages of syphilis, and therefore it is of great importance that the real nature of these products should be ascertained.

Two views have hitherto been advanced, (1) that silver salvarsan and sodium silver salvarsan \* are co-ordination compounds, (2) that sodium silver salvarsan is a mixture containing colloidal silver. Ehrlich and Karrer (*Ber.*, 1915, 48, 1634) considered that salvarsan formed an additive compound (I) with two molecules of silver nitrate, in which the silver was attached by residual valency to the arsenic :



Karrer (*Ber.*, 1919, 52, 2321) still maintains this, and states that sodium silver salvarsan is formed simply by replacement of the phenolic hydrogen by sodium. Binz and his collaborators (*Arb.*

\* For convenience, the author here uses the names "sodium silver salvarsan" and "silver salvarsan" to distinguish between the alkalisated and non-alkalisated reaction products of salvarsan and silver nitrate.



*Inst. exper. Ther. Georg Speyer-Hause*, 1919, 8, 25; *Ber.*, 1920, 53, [B], 416), on the contrary, considered that the silver was attached to nitrogen as in (II), but have recently suggested that there are two series of compounds, one in which silver is attached to nitrogen, the other in which it is attached to arsenic (*Ber.*, 1922, 55, [B], 3826). The possibility, on the other hand, that the dark-coloured sodium silver salvarsan might contain colloidal silver was suggested by Kolle (*Deut. med. Woch.*, 1918, 1177) and investigated by Bauer (*Arb. Inst. exper. Ther. Georg Speyer-Hause*, 1919, 8, 45; *Ber.*, 1920, 53, [B], 416), who found that the solution passed unchanged through parchment paper and collodion membranes and concluded that colloidal silver was not present, and by Raiziss and Gavron (*J. Pharm. Exper. Ther.*, 1922, 20, 163), who obtained the contrary result, arsenic passing the parchment but no silver, and suggested that sodium silver salvarsan was a mixture of sodium salvarsan and colloidal silver.

The author has for some time been investigating the nature of silver salvarsan and sodium silver salvarsan, in solutions in methyl alcohol as used by Ehrlich and Karrer, and aqueous solutions as used by Binz.

In solutions in methyl alcohol, it was found that if an excess of ether were used for precipitation, as is customary in the salvarsan series, a solid could be obtained from the reaction mixture of diaminodihydroxyarsenobenzene hydrochloride and silver nitrate having the same silver-content as that of Ehrlich and Karrer, who did not state the amount of ether taken. If, however, the alcoholic solution were added to a comparatively small quantity of ether, a solid, soluble in water, was precipitated which contained arsenic, silver, and chlorine in the atomic ratios 2 : 7.1 : 6.4. This contains more silver and less arsenic than could correspond to a co-ordination compound; it therefore consists of colloidal silver chloride, reversibly soluble owing to the small amount of arsenic compound now precipitated with it, the chief constituent of which is probably the hitherto undescribed diaminodihydroxyarsenobenzene dinitrate. This view receives support by the observation that in more concentrated methyl-alcoholic solutions, if the alcohol were dry, silver chloride was precipitated without the addition of ether. Under similar experimental conditions, solutions of sodium silver salvarsan in methyl alcohol yielded colloidal silver oxide, reversibly soluble in water.

In the case of aqueous solutions, emphasis has been laid by previous workers on the difficulty of investigating the interaction of salvarsan and silver nitrate owing to the similar solubility of all the substances concerned. Binz, Bauer, and Hallstein (*Arb.*

*Inst. exper. Ther. Georg Speyer-Hause*, 1919, 8, 25) could not, for this reason, elucidate the nature of a solution containing two molecular proportions of silver nitrate. It is now found that all the silver is removed from aqueous solutions of both silver salvarsan and sodium silver salvarsan by aqueous picric acid, owing to the simultaneous precipitation of the diaminodihydroxyarsenobenzene as an insoluble picrate. From the solid products so obtained, the picrate is readily removed by acetone, leaving solids rich in silver chloride and silver oxide, respectively, but containing only a small amount of arsenic. Like Paal's colloidal silver, precipitated by acid from sols containing sodium protalbinat or lysalbinat (*Ber.*, 1902, 35, 2224), these are insoluble in water but soluble in alkali.

In the case of sodium silver salvarsan, it is probable that colloidal silver is present as well as silver oxide, for a comparatively large amount of arsenic is not precipitated by picric acid, indicating that oxidation of the salvarsan by the silver oxide has occurred; whereas in the case of silver salvarsan the percentage of arsenic precipitated is the same as in the case of salvarsan alone. The oxidation products of salvarsan, 3-amino-4-hydroxyphenylarsenious oxide and the corresponding acid, are not precipitated by picric acid under these conditions.

The above results obtained with silver salvarsan and with sodium silver salvarsan, both in aqueous and alcoholic solution, seem to indicate conclusively that to the properties of diaminodihydroxyarsenobenzene and its salts as protective colloids must be ascribed the phenomena observed in their reactions with silver nitrate. In the case of silver salvarsan, silver chloride is formed by double decomposition and remains in solution, being protected by the diaminodihydroxyarsenobenzene dinitrate, but not essentially in stoichiometric proportions. In the case of sodium silver salvarsan, the silver is present as oxide and probably to some extent as metal, both again being protected by the colloidal sodium salvarsan as suggested by Raiziss and Gavron (*loc. cit.*), or by its hydrolytic product, "salvarsan base." The occurrence of some combination is not excluded by these results, but the double decomposition appears to form the predominating part of the reaction.

Contrary to the representation by Ehrlich and Karrer of the material obtained by them as a silver nitrate additive product, it follows that it is a mixture of two molecules of silver chloride and one of diaminodihydroxyarsenobenzene dinitrate; such a mixture would have the silver content observed by them. The precipitate obtained from this by Karrer (*Ber.*, 1919, 52, 2323) on addition of sulphuric acid and considered by him to be a sulphate of the co-ordination compound is equally well explained as a mixture of



diaminodihydroxyarsenobenzene sulphate with two molecules of silver chloride.

With regard to the statement of Binz and Ludwig (*Ber.*, 1922, 55, [B], 3826), that oxidation occurs if more than one molecular proportion of silver nitrate be added to salvarsan, which does not, however, appear to arise out of the results described by them, no difference in the nature of the reaction in alcoholic solution was observed when one or two molecules were taken; in aqueous solution, oxidation did not occur when two molecules of silver nitrate were used.

Complete analyses of some specimens of commercial sodium silver salvarsan are given in the experimental part. It is seen that they differ from those made from salvarsan in containing sulphate instead of chloride. A specimen corresponding in composition to the commercial product, however, behaved in a similar manner to those described above when treated with picric acid and acetone.

#### EXPERIMENTAL.

*Isolation of Colloidal Silver Chloride from Methyl-alcoholic Silver Salvarsan Solutions.\**—(a) *Two molecules of silver nitrate.* 2.16 Grams of silver nitrate were dissolved in 105 c.c. of dry methyl alcohol and added to a solution of 3 grams of salvarsan in 52 c.c. of methyl alcohol. The deep red solution obtained was added in a thin stream to 170 c.c. of dry ether. After shaking well, the granular precipitate was filtered, washed with ether, and dried in a vacuum desiccator (yield 2.3 grams). It formed a brown powder, soluble in water with the exception of a very slight residue, less soluble in methyl alcohol, soluble to a clear dark brown solution in aqueous sodium hydroxide (Found: Ag = 51.18; As = 10.04; N = 3.06; Cl = 15.47 per cent. Atomic ratio Ag : As = 7.1 : 2; N : As = 3.3 : 2; Cl : Ag = 0.9 : 1).

With regard to the nature of the arsenic compound present here together with silver chloride, the ratio of nitrogen to arsenic suggests that it partly consists of salvarsan nitrate (see p. 641). The remainder is probably salvarsan base, since the whole of the arsenic was present in the arseno-form, being precipitated from an aqueous solution of the substance by picric acid. One gram was dissolved in water, centrifuged clear from a trace of solid, and added to 100 c.c. of 1 per cent. aqueous picric acid, cooled in ice. The granular, brown product was filtered and dried (Found: Ag = 44.4; As = 8.61; Cl = 13.2 per cent. Ag : As = 7.17 : 2; Cl : Ag = 0.9 : 1). The filtrate contained no silver. The fact that the ratio of chlorine

\* Throughout these experiments the air was displaced by nitrogen.



to silver is unchanged is additional evidence that the silver was present as silver chloride.

The alcohol-ether filtrate from the above precipitation by ether was poured into 690 c.c. of ether. 1.68 Grams of a lighter-coloured solid were obtained (Found : Ag = 3.71; Cl = 0.55; As = 27.16; N = 9.31. Ag : As = 0.19 : 2; N : As = 3.7 : 2. Salvarsan dinitrate made from the above salvarsan, mixed with 4.9 per cent. of silver chloride, requires As = 27.16 per cent.; N : As = 3.9 : 2).

(b) *One molecule of silver nitrate.* 1.08 Grams of silver nitrate were dissolved in 52 c.c. of methyl alcohol and added to 3 grams of salvarsan, dissolved in 52 c.c. of methyl alcohol. The clear red solution was added to 79 c.c. of dry ether cooled to 0°, and the precipitate filtered, washed with ether, and dried (yield 1.3 grams) (Found : Ag = 37.87; As = 16.19; Cl = 15.15 per cent. Ag : As = 3.25 : 2; Cl : Ag = 1.2 : 1). The ratio Ag : As is too high for a co-ordination compound, as before, and the ratio Cl : Ag shows the presence of silver chloride.

The filtrate was added to 1000 c.c. of ether. 2.1 Grams of solid were obtained, containing only a small quantity of silver, and arsenic corresponding to salvarsan dinitrate as before (Found : Ag = 5.65; As = 27.33 per cent.).

*Isolation of Colloidal Silver Oxide from Methyl Alcoholic Sodium Silver Salvarsan Solution.*—2.15 Grams of silver nitrate were dissolved in 105 c.c. of methyl alcohol and added to a mixture of 3 grams of salvarsan in 52 c.c. of methyl alcohol and 11.7 c.c. of 20 per cent. methyl-alcoholic sodium hydroxide. A solid separated, which was at first overlooked owing to its fineness of division and the intense colour of the solution; this was centrifuged off and dried in a vacuum (yield = 0.7 gram). It formed a black powder with metallic lustre, readily soluble in water to a clear dark brown solution, and effervescing slowly when treated with hydrazine hydrate (Found : Ag = 78.4; As = 5.1 per cent. Ag : As = 21.2 : 2).

*Isolation of Colloidal Silver Chloride from Aqueous Silver Salvarsan Solution.*—2.57 Grams of silver nitrate (2 mols.) were dissolved in 152 c.c. of water and added to 3.65 grams of salvarsan in 300 c.c. of water. The clear deep red solution formed was added to 6.2 grams of picric acid dissolved in 620 c.c. of water, and the precipitate washed by decantation and dried in a vacuum desiccator (yield 6.7 grams). It formed a brown powder (Found : Ag = 23.56; As = 14.70 per cent. Ag : As = 2.2 : 2). The filtrate contained no silver. From the above figures, 88.1 per cent. of the arsenic taken is present in the picric acid precipitate. This is in good agreement with the corresponding figure (86.5 per



cent.) for the precipitation of diaminodihydroxyarsenobenzene picrate alone (below); it follows that oxidation of the salvarsan by the silver nitrate had not occurred.

*Extraction of the Picric Acid Precipitate with Acetone.*—Two grams were shaken with 7.5 c.c. of acetone containing 5 per cent. of water. A large portion immediately dissolved, leaving a light yellow solid, which was centrifuged off, washed in the tube with another 7.5 c.c. of acetone, which was now only slightly coloured, and dried in a vacuum desiccator (yield 0.4 gram). It formed a faintly yellow powder (Found: Ag = 62.65; As = 3.47; Cl = 20.32. Ag : As = 25.1 : 2; Cl : Ag = 0.99 : 1; AgCl = 83.2 per cent.). On further washing with acetone, it tended to pass into colloidal solution.

*Isolation of Colloidal Silver Oxide from Aqueous Sodium Silver Salvarsan Solution.*—2.15 Grams of silver nitrate were dissolved in 12 c.c. of water and added to a solution of 3 grams of salvarsan in 65 c.c. of water and 3.4 c.c. of 45 per cent. sodium hydroxide. The clear dark solution was added to a solution of picric acid (excess), made by dissolving 9.2 grams of picric acid in 420 c.c. of hot water and cooling just before use. The mixture was well shaken and the granular precipitate washed and dried in a vacuum desiccator (yield 4.23 grams). It formed a dark solid, partly soluble in acetone (Found: Ag = 30.3; As = 13.9 per cent. Ag : As = 3.03 : 2. The ratio Ag : As in the quantities taken = 1 : 1). The filtrate contained no silver. The ratio of silver to arsenic is here increased to a markedly greater extent than in the corresponding precipitation of silver salvarsan (p. 639). This implies that part of the salvarsan has here been oxidised at the double bond by the silver oxide, since the oxidation products would not be precipitated, and it follows that the solid colloidal product obtained below partly consists of colloidal silver.

*Extraction of the Picric Acid Precipitate with Acetone.*—Two grams were shaken with 7.5 c.c. of acetone, and the undissolved portion centrifuged off and washed twice by shaking with a similar quantity of acetone and centrifuging (yield 0.4 gram). It formed a black powder, insoluble in water but readily soluble in dilute alkali to a deep brown solution (Found: Ag = 84.92; As = 2.99; Cl = 1.28 per cent.). It caused slow effervescence in hydrazine hydrate, and therefore contained silver oxide; the presence of colloidal silver also is probable owing to the observed oxidation of the salvarsan. On further washing with acetone, it tended to pass into colloidal solution, but not so readily as the silver chloride (above).

*3 : 3'-Diamino-4 : 4'-dihydroxyarsenobenzene Dipicrate.*—One gram



of salvarsan was dissolved in 100 c.c. of water at  $0^{\circ}$  and treated with 100 c.c. of 1 per cent. aqueous picric acid solution at  $0^{\circ}$ . The suspension was shaken well and the granular precipitate washed by decantation and dried in a vacuum desiccator (yield, 86.5 per cent. of the theoretical). It forms a deep yellow powder, sparingly soluble in water, moderately soluble in ethyl alcohol, and readily soluble in methyl alcohol, or acetone containing a small quantity of water; m. p.  $142^{\circ}$  (corr.) with decomposition (Found: As = 18.6; N = 12.8. Atomic ratio N : As = 7.4 : 2.  $C_{24}H_{18}O_{16}N_8As_2$  requires As = 18.2; N = 13.6 per cent. The ratio N : As in the salvarsan used, however, was 1.9 : 2, a number of specimens of salvarsan examined, which had been made by the usual commercial method, agreeing in this respect. A dipicrate made from this salvarsan requires N : As = 7.6 : 2).

*3 : 3'-Diamino-4 : 4'-dihydroxyarsenobenzene Dinitrate*.—1.96 Grams of salvarsan base, made by Christiansen's method (*J. Amer. Chem. Soc.*, 1921, **43**, 2207), were dissolved in 20 c.c. of dry methyl alcohol containing the theoretical quantity of nitric acid. The clear solution was poured into 400 c.c. of dry ether, and the solid obtained filtered, washed with ether, and dried in a vacuum desiccator (yield = 2.3 grams). It formed a pale yellow, granular solid, readily soluble in water, methyl alcohol, or ethyl alcohol, and decomposing on heating without melting (Found: As = 28.3; N = 10.35. N : As = 3.9 : 2.  $C_{12}H_{12}O_2N_2As_2 \cdot 2HNO_3 \cdot 2H_2O$  requires As = 28.4; N = 10.6 per cent.). It was precipitated by dilute sulphuric and picric acids and, like salvarsan, gave an orange coloration with *p*-dimethylaminobenzaldehyde.

#### *The Composition of Commercial Sodium Silver Salvarsan.*

Specimens of the commercial product from three countries gave the following percentage results, corrected for loss of weight in a vacuum desiccator.

Speci- men.	Loss in a vacuum.	Ag.	As.	Na.	S (total).	S (sul- phate).	C.	H.	N.	Cl.
1	4.27	14.05	21.63	10.39	4.53	4.00	21.94	2.50	4.11	0.15
2	9.81	18.04	22.13	10.85	3.63	2.12	22.40	2.77	4.36	0.22
3	8.72	13.3	19.98	12.83	5.12	4.0	19.11	2.58	4.00	0.38

#### *The Analytical Method Employed.*

The method described by Binz, Bauer, and Hallstein (*Ber.*, 1920, **53**, [B], 426) was tried, but discarded in favour of the following, which was found to be more rapid and exact. 0.2 Gram of the substance is mixed in a flask with 2 grams of powdered potassium

permanganate and 10 c.c. of water. Ten c.c. of concentrated sulphuric acid are then gradually added and the mixture is warmed gently for fifteen minutes. Oxalic acid solution is next added until the colour is removed, and if silver is present this is now precipitated and removed as usual. The filtrate is evaporated to a volume of 60 c.c. and the arsenic estimated iodometrically.

If the substance to be examined is a picrate, it is necessary to remove completely the oxides of nitrogen resulting from the oxidation, otherwise the arsenic result may be slightly high. This is satisfactorily done by transferring the mixture to a beaker after the addition of oxalic acid, boiling gently for fifteen minutes, retransferring to the flask and diluting to 150 c.c. with water. The contents of the flask are now evaporated down to 60 c.c. and proceeded with as before. The figures marked with an asterisk in the following table are examples of the results obtained by this method :

Pure silver nitrate .....	Ag = 63.22, 63.05 (thiocyanate); 63.20*.
Silver salvarsan .....	Ag = 13.29; As = 20.04 (Carius); Ag = 13.24*; As = 19.55*.
„ „ another sample	As = 15.97 (Carius); 16.14*.
Picric acid precipitate (p. 639)	Ag = 30.28; As = 13.88 (Carius); Ag = 30.22*; As = 13.88*.

Chlorine was estimated by the Carius method in all cases.

In conclusion, the author would like to express his gratitude to Dr. T. A. Henry for his interest and valuable advice, and to Mr. W. Ramsay for assistance in the considerable amount of analytical work which has been involved.

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[Received, February 15th, 1923.]







